

PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Docket No: Q86357

Tetsuro KIKUCHI, et al.

Appln. No.: 10/540,577

Group Art Unit: 1614

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Examiner: Savitha M RAO

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For: CARBOSTYRIL DERIVATES AND SEROTONIN REUPTAKE INHIBITORS FOR
TREATMENT OF MOOD DISORDERS

DECLARATION UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
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Sir:

I, Tsuyoshi HIROSE, hereby declare and state:

THAT I am a citizen of Japan, residing at 8-9-502, Sakoichiban-cho, Tokushima-shi 770-0021;

THAT I have received the degree of Ph. D. of Medicinal Science in 2005 from Nagoya University School of Medicine;

THAT I have been employed by Otsuka Pharmaceutical Co., Ltd., since 1984, where I hold a position as Leader, with responsibility for planning, conducting, and interpreting studies of pharmaceutical compounds, in particular those discussed in this declaration.

In order to show the unexpectedly superior effects of the present invention, the following comparative experiment was conducted by me or under my supervision.

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In the comparative experiment, dehydroaripiprazole and escitalopram were selected as the metabolite of aripiprazole and the SRI, respectively. Escitalopram is one of the enantiomers (S-enantiomeric form) of the racemic body scitalopram and was known to have a similar pharmacological effect as escitalopram at the time of the priority date of the present application.

As the combined agents to be compared, those disclosed in Examples 1 and 2 of Wong et al, i.e., a combination of a neuroleptic (risperidone, olanzapine, clozapine) and an NRI (reboxetine) were selected.

THE EVALUATION OF ANTIDEPRESSIVE EFFECTS IN FORCED SWIMMING
TEST IN MICE

[Materials and method]

The following were used as the present inventive combination:

aripiprazole and six SRIs (duloxetine, venlafaxine, milnacipram, escitalopram, paroxetine, sertraline);

dehydroaripiprazole and an SRI (escitalopram); and

The following were used as the comparative combination of the three antipsychotic agents (risperidone, olanzapine, clozapine) and the NRI (reboxetine), respectively.

A forced swimming test was employed, which is an animal model devised by Porsolt et al¹ for evaluating anti-depressive effects of an agent. An animal (a mouse) is put in a cylindrical tank of 9 cm in diameter and 25 cm in height filled with water (temperature at 24 to 25 °C) of 13 cm in depth. The mouse falls into an immobilized state after a while, the duration of which is

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shortened by administration of an anti-depressive agent in advance. The shortened degree of the immobility time is evaluated as an index of the anti-depressive effect. The test is widely used as an experimental animal model test which can reflect clinical anti-depressive effects.

The purpose of the test was to compare the effects of the combination of aripiprazole and six SRIs (duloxetine, venlafaxine, milnacipram, escitalopram, paroxetine, and sertraline) and dehydroaripiprazole and an SRI (escitalopram) versus the combination of the three antipsychotic agents (risperidone, olanzapine, and clozapine) and the NRI (reboxetine) on the immobility time.

As the animal, ICR male mice (five to six week-old) were used. Each of the NRIs and SRIs, antipsychotic agents and dehydroaripiprazole or vehicles were administered to the mice before the beginning of the test; the mice were put in the cylindrical water tank and the immobility time after two to four minutes from the start of swimming action was measured by an activity measurement apparatus equipped with a passive type infra-red ray detection sensor (Supermex[®], Muromachi Kikai Co., Ltd.) integrated with an analytic program for forced swimming.

Aripiprazole and dehydroaripiprazole were dissolved in 0.1 % acetic acid-saline and 10% dimethylformamide-saline, respectively; each of the NRIs and SRIs were suspended or dissolved in 5% gum arabic-distilled water for use. Each of the SRI and NRIs (duloxetine (10 mg), milnacipram (30 mg), venlafaxine (10 mg), escitalopram (10 mg), paroxetine (10 mg), sertraline (3 mg) and the antipsychotic agents (risperidone (0.1 mg), olanzapine (3 mg), clozapine (10 mg)) were orally administered 60 minutes before the test start; aripiprazole (0.01 mg) and

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dehydroaripiprazole (0.01 mg) were intraperitoneally administered 15 minutes before the test start.

¹Porsolt RD, Bertin A, Jalfre M: Arch Int. Pharmacodyn. Ther. 1977 229(2): 327-36.

[Results and discussion]

The results are shown in Tables 1-3 below.

Table 1 Effects of the combined treatment of aripiprazole and each SRI on immobility time of forced swimming test in mice

| Treatment 1 | Dose (mg/kg) | Treatment 2 | Dose (mg/kg) | N | Immobility time during 2 to 4 min after beginning of swimming Unit: sec (mean±S.E.M) |
|--------------|--------------|--------------|--------------|---|--|
| Vehicle 1 | 0 | Vehicle 2 | 0 | 6 | 69.1 ± 9.1 |
| aripiprazole | 0.01 | Vehicle 2 | 0 | 6 | 85.0 ± 8.2 |
| Vehicle 1 | 0 | duloxetine | 10 | 6 | 85.9 ± 18.1 |
| aripiprazole | 0.01 | duloxetine | 10 | 6 | 44.8 ± 7.3 * |
| Vehicle 1 | 0 | Vehicle 2 | 0 | 6 | 85.3 ± 7.5 |
| aripiprazole | 0.01 | Vehicle 2 | 0 | 6 | 94.9 ± 8.0 |
| Vehicle 1 | 0 | venlafaxine | 10 | 6 | 84.8 ± 11.0 |
| aripiprazole | 0.01 | venlafaxine | 10 | 6 | 56.1 ± 5.6 * |
| Vehicle 1 | 0 | Vehicle 2 | 0 | 6 | 69.2 ± 8.4 |
| aripiprazole | 0.01 | Vehicle 2 | 0 | 6 | 73.0 ± 10.1 |
| Vehicle 1 | 0 | milnacipram | 30 | 6 | 63.8 ± 7.8 |
| aripiprazole | 0.01 | milnacipram | 30 | 6 | 43.0 ± 7.6 * |
| Vehicle 1 | 0 | Vehicle 2 | 0 | 6 | 76.9 ± 12.6 |
| aripiprazole | 0.01 | Vehicle 2 | 0 | 6 | 56.3 ± 5.7 |
| Vehicle 1 | 0 | escitalopram | 10 | 6 | 53.8 ± 8.6 |
| aripiprazole | 0.01 | escitalopram | 10 | 6 | 46.2 ± 4.6* |
| Vehicle 1 | 0 | Vehicle 2 | 0 | 6 | 57.3 ± 5.7 |
| aripiprazole | 0.01 | Vehicle 2 | 0 | 6 | 47.2 ± 3.4 |
| Vehicle 1 | 0 | paroxetine | 10 | 6 | 47.3 ± 8.5 |
| aripiprazole | 0.01 | paroxetine | 10 | 6 | 27.3 ± 4.0 * |
| Vehicle 1 | 0 | Vehicle 2 | 0 | 6 | 62.6 ± 7.2 |
| aripiprazole | 0.01 | Vehicle 2 | 0 | 6 | 54.5 ± 6.5 |
| Vehicle 1 | 0 | sertraline | 3 | 6 | 55.8 ± 8.4 |
| aripiprazole | 0.01 | sertraline | 3 | 6 | 36.4 ± 5.9 * |

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Aripiprazole and vehicle (vehicle 1: 0.1% acetic acid-saline) were intraperitoneally injected 15 minutes before the start of the test. Each SRI and vehicle (vehicle 2: 5% gum Arabic-distilled water) were orally administered 1 hr before the start of the test. Immobility time was measured using an activity measurement apparatus equipped with a passive type infra-red ray detection sensor (Supermex[®], Muromachi Kikai Co., Ltd.).

*p<0.05 vs. corresponding vehicle 1 and Vehicle 2 treated group (two-tailed t-test).

Table 2 Effects of combined treatment of antidepressant Reboxetine and each atypical antipsychotic on immobility time of forced swimming test in mice.

| Treatment 1 | Dose (mg/kg) | Treatment 2 | Dose (mg/kg) | N | Immobility time during 2 to 4 min after beginning of swimming Unit: sec (mean±S.E.M.) |
|-------------|--------------|-------------|--------------|---|---|
| Vehicle | 0 | Vehicle | 0 | 6 | 68.9 ± 10.9 |
| Risperidone | 0.1 | Vehicle | 0 | 6 | 67.0 ± 11.7 |
| Vehicle | 0 | Reboxetine | 10 | 6 | 56.0 ± 8.4 |
| Risperidone | 0.1 | Reboxetine | 10 | 6 | 69.3 ± 10.0 |
| Vehicle | 0 | Vehicle | 0 | 6 | 81.4 ± 7.9 |
| Olanzapine | 3 | Vehicle | 0 | 6 | 105.4 ± 16.2 |
| Vehicle | 0 | Reboxetine | 10 | 6 | 59.6 ± 15.7 |
| Olanzapine | 3 | Reboxetine | 10 | 6 | 110.4 ± 12.5 |
| Vehicle | 0 | Vehicle | 0 | 6 | 64.2 ± 11.5 |
| Clozapine | 10 | Vehicle | 0 | 6 | 69.2 ± 14.2 |
| Vehicle | 0 | Reboxetine | 10 | 6 | 54.8 ± 12.0 |
| Clozapine | 10 | Reboxetine | 10 | 6 | 68.3 ± 7.3 |

Reboxetine and each antipsychotic and vehicles (5% gum Arabic-distilled water) were orally administered 1 hr before the start of the test. Immobility time was measured using an activity measurement apparatus equipped with a passive type infra-red ray detection sensor (Supermex[®], Muromachi Kikai Co., Ltd.).

Table 3 Effects of combined treatment of dehydroaripiprazole and escitalopram on immobility time of forced swimming test in mice.

| Treatment 1 | Dose (mg/k) | Treatment 2 | Dose (mg/k) | N | Immobility time during 2 to 4 min after beginning of swimming Unit: sec (mean±S.E.M) |
|---------------------|-------------|--------------|-------------|---|--|
| Vehicle 1 | 0 | Vehicle 2 | 0 | 8 | 99.4 ± 8.3 |
| dehydroaripiprazole | 0.01 | Vehicle 2 | 0 | 8 | 92.6 ± 7.8 |
| Vehicle 1 | 0 | escitalopram | 10 | 8 | 96.3 ± 11.0 |

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| | | | | | |
|---------------------|------|--------------|----|---|--------------|
| dehydroaripiprazole | 0.01 | escitalopram | 10 | 8 | 67.1 ± 8.2 * |
|---------------------|------|--------------|----|---|--------------|

Dehydroaripiprazole and vehicle (vehicle 1: 10% dimethylformamide-saline) were intraperitoneally injected 15 minutes before the testing. Escitalopram and vehicle (vehicle 2: 5% gum Arabic-distilled water) were orally administered 1hr before the testing. Activities of animals were measured by using Supermex® (activity measurement apparatus; Muromachi Kikai Co., Ltd., Tokyo, Japan) attached with a passive type of infra-red ray detection sensor.

As it can be seen from the above results, the inventive combination of the present invention (aripiprazole and duloxetine, venlafaxine milnacipram, escitalopram, paroxetine or sertraline, and dehydroaripiprazole and escitalopram) clearly shorten the prolonged immobility time in the forced swimming test of mice (which means that the inventive combinations have antidepressive effects). On the other hand, the combinations described in Wong et al (risperidone, olanzapine or clozapine and reboxetine) did not significantly shorten the prolonged immobility time in the forced swimming test of mice (which means that the combinations of Wong et al tend to deteriorate). Therefore, the combination of the present invention which is not disclosed in Wong et al (for example, the combinations of aripiprazole and duloxetine, venlafaxine, milnacipram, escitalopram, paroxetine or sertraline, and dehydroaripiprazole and escitalopram) have synergistic effects which are completely unexpected from Wong et al.

Claim 5 of Wong et al describes 41 antipsychotic agents other than aripiprazole. Further, claim 2 describes 15 NRIs. Thus, combinations of an antipsychotic agent and an NRI can be at least 630. Wong et al does not disclose at all the selection of duloxetine, venlafaxine and milnacipran from the 15 NRIs and aripiprazole from 42 antipsychotic agents. Accordingly, it would not have been easily conceivable for one skilled in the art to achieve the claimed invention from the at least 630 combinations.

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Further, the above additional pharmacological tests reveal that the combinations of the present invention which are not specifically disclosed in the cited references (the combinations of agents such as aripiprazole and duloxetine, venlafaxine, milnacipran, escitalopram, paroxetine, or sertraline, and dehydroaripiprazole and escitalopram) have synergistic effects unexpected from the specific combination disclosed in Wong et al. Wong et al does not describe nor suggest the combination of agents of the present invention. Therefore, the present invention possesses is patentable over the cited references.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: Mar. 2, 2009

Tangdi Line